Excitability and action potential in human axons

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This abstract concerns studies of axonal excitability in human subjects, focusing on the role of two depolarizing currents, using measures of the physiological consequences of their activity.

The only identified Na^+ channel isoform at the healthy mature node of Ranvier is Nav1.6 but it can have two gating modes: transient (~98-99% of the total Na^+ conductance) and persistent (~1-2% of the total Na^+ conductance). The persistent current is greater in sensory axons than motor, but sensory axons are ~4 mV more depolarized than motor, and this is sufficient to account for the greater INaP on sensory axons. The hyperpolarization-activated current (Ih) is internodally located, passes a depolarizing current, dependent on HCN channels ("hyperpolarization-activated, cyclic nucleotide-gated"). It contributes to resting membrane potential, at least in low-threshold motor axons, and faster isoform(s) of Ih is (are) more active on sensory axons than motor.

The persistent Na^+ current may not be the reason why some axons have a reproducibly low threshold: instead, low-threshold axons have a low threshold in part because of greater expression of HCN channels. The apparently greater inward rectification on sensory axons than motor could be due to different isoforms with different kinetics rather than a greater total Ih. HCN current could be active at rest and could contribute to resting membrane potential.

In the genetic channelopathies, episodic ataxia type 1 (due to a mutation in the KCNA1 gene encoding Kv1.1 subunit of the fast K^+ channel) and benign familial neonatal epilepsy due to a mutation in the KCNQ2 gene encoding Kv7.2), the same mutated ion channel is expressed on central and peripheral axons, and there are characteristic changes in axonal excitability.

In acquired diseases, there are plastic changes in the properties of motor axons in peripheral nerves, *e.g.* in stroke, there is less in Ih. Here the axonal changes are secondary, presumably reflecting changes in membrane potential or adaptive change in motoneurone properties.